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Probing salicylamide bioisosteric replacement in the design of *Plasmodium Falciparum* dihydroorotate dehydrogenase (*pf*DHODH) inhibitors.

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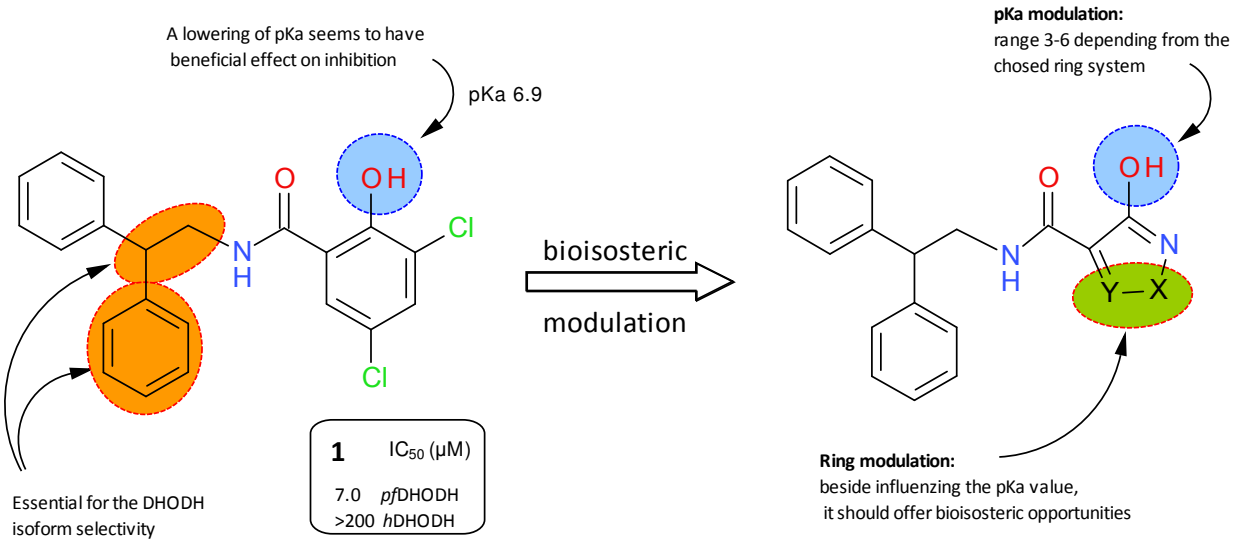
Malaria causes great suffering with estimated annual mortalities of over 800.000 people, principally in Africa and Asia. A major problem in the fight against malaria is resistance to current drug treatments and several strategies have been employed to combat this problem. Beside these, inhibitors of the newly validated target *dihydroorotate dehydrogenase* (DHODH) could play an important role as future single or combinatory treatment of malaria. A continuing program of ours investigates *Plasmodium Falciparum* dihydroorotate dehydrogenase (*pf*DHODH) inhibitors based on N-substituted salicylamides scaffold.[1] Recently, the most active model of the series (**1**) showed low micromolar range activity over *pf*DHODH together with a quite interesting selectivity over human DHODH (*h*DHODH).[1]

Isosteric replacement is a widely used approach within *Medicinal Chemistry* for improving properties of a lead compound such as bioavailability, selectivity, and potency.[2] Since 2006, the *Med Chem* group at *DSTF* directed its efforts towards the investigation of hydroxylated pentatomic heterocyclic systems in order to create a sophisticate tool able to iso/bioisosterically mimic the carboxylic group, both electronically and sterically.[3] More recently, attentions were directed in the application of this technology to other acidic systems.[4]

In this poster, the salicylamide moiety of highly selective *pf*DHODH where identified as a possible occasion for a bioisosteric modulation. The synthesis, the dissociation constant (pKa) as well as the preliminary *pf*DHODH *in vitro* inhibition assays are presented and discussed.



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